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## **Clinical use of the beta-3 adrenoceptor agonist mirabegron in patients with overactive bladder syndrome**

### **Abstract**

Mirabegron is a beta-3 adrenoceptor agonist licensed for the treatment of overactive bladder symptoms, such as urinary urgency or urgency incontinence. Beta-3 adrenoceptor activation causes detrusor muscle relaxation, but mirabegron may also act by binding other targets in the bladder, and it may also reduce activity in sensory nerves. Phase 3 clinical trials (SCORPIO, ARIES, and CAPRICORN) evaluated mirabegron at various doses, demonstrating reduction from baseline to endpoint in mean incontinence episodes and mean number of micturitions per 24 hours (co-primary endpoints), along with health related quality of life and a range of secondary measures. Efficacy was seen in many patients who had previously discontinued antimuscarinic therapy on the grounds of lack of efficacy or poor tolerability. Treatment emergent adverse effects were documented in a long-term study (TAURUS), mostly being of mild or moderate severity. The most frequent adverse effects were hypertension, dry mouth, constipation, and headache, with a lower incidence of dry mouth than for the antimuscarinic active comparator. Efficacy and safety is not substantially different in older patients. A urodynamic safety study in men showed no consistent effect on voiding function, but a small increase in post void residual. Use of mirabegron in combination with alpha-adrenergic blockers does not appear to increase adverse effects. Dose reduction is needed in people with severe renal failure, or

moderate hepatic failure. Dose adjustment is not needed in relation to food intake. Ongoing research is evaluating the potential for combination therapy with antimuscarinics.

## Introduction

Lower urinary tract symptoms (LUTS) affecting urine storage include urinary urgency, urgency incontinence, increased daytime frequency and nocturia <sup>1</sup>. Overactive bladder syndrome (OAB) is defined by the International Continence Society (ICS) as urinary urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia in the absence of proven infection or any other pathology <sup>2</sup>. It is a chronic symptom complex that can substantially impair quality of life (QoL). The prevalence of LUTS <sup>3</sup>, OAB and urgency urinary incontinence is substantial, affecting both women and men, and resulting in considerable morbidity, personal cost and health economic burden <sup>4, 5</sup>.

Initial management uses conservative measures, such as fluid advice and bladder training <sup>6</sup>. Drug therapy using antimuscarinics has long been the mainstay of the pharmacological treatment of OAB <sup>6-8</sup>. However, compliance with these drugs is generally poor <sup>9</sup>, due to perceived lack of efficacy and potential high rate of side effects. The emergence of new drugs and treatment regimens should improve patient persistence with treatment and acceptability. Development of Mirabegron (YM178), a  $\beta_3$ -adrenoceptor (AR) agonist now offers a new pharmacotherapy option for the treatment of OAB <sup>10</sup>. Mirabegron is available for clinical use as a modified release film coated tablet in an Oral Controlled Absorption System (OCAS), with two licensed dosage strengths of 25 mg and 50 mg.

## Mechanism of Action

There are three sub-types of  $\beta$ -AR, with the  $\beta_3$ -AR predominating in the detrusor muscle of some species <sup>11</sup>, including the human bladder.  $\beta_3$ -AR constitutes a high proportion of the  $\beta$ -AR mRNA in the human detrusor <sup>12</sup>. Activation of these receptors elicits detrusor relaxation in bladder strips from various species <sup>13</sup>, through generation of cyclic adenosine monophosphate <sup>13, 14</sup>.  $\beta_3$ -AR may also be present in other cell types of the bladder, such as urothelium <sup>14-16</sup> or interstitial cells <sup>14</sup>. However, the role of their activation in the urothelium remains to be established <sup>17</sup>.

In animal studies, activation of  $\beta_3$ -AR gives dose-dependent detrusor relaxation during the storage phase of the micturition cycle. Functionally, it increases intervoid interval and bladder compliance, while preserving voiding function in a rodent model <sup>18</sup>.  $\beta_3$ -AR are also suggested to inhibit sensory nerve activation, including activity in mechano-sensitive A-delta fibres <sup>19</sup>, and also reducing autonomous non voiding contractions <sup>18, 20</sup>.  $\beta$ -AR activation can elicit release of nitric oxide by urothelium, giving a potential indirect mechanism which could further contribute to bladder relaxation <sup>21, 22</sup>. A critical influence of  $\beta_3$ -ARs in increasing bladder capacity, without changing micturition pressure or residual volume, may be mediated by inhibition of afferent nerve fibre activity <sup>23</sup>.

## Pharmacokinetics-

The marketed formulation of mirabegron is in an oral controlled absorption system (OCAS), with oral bioavailability in the range of 24 - 53% <sup>24</sup>. The plasma protein binding is 71% <sup>25</sup>. The time to reach maximum concentration after dosing is 3-4 hours, and the terminal elimination half-life is approximately 50 hours. The

absolute bioavailability is dose-dependent and affected by gender <sup>24</sup>. Interactions with cytochrome P450 (CYP) metabolism <sup>26 27</sup> are potentially relevant clinically. For example, drug-drug interactions may occur with concomitant administration of drugs that exert inducible (rifampin) or inhibitory (ketoconazole) effect on CYP3A4/5 <sup>24</sup>. CYP2D6 inhibition by mirabegron might alter the plasma exposure of metoprolol <sup>24</sup>. One study has shown that combining mirabegron with an alpha adrenergic antagonist (tamsulosin) did not affect safety aspects, notably cardiovascular adverse effects, in 48 healthy men aged 44 years or older <sup>28</sup>.

Mirabegron OCAS tablets show a decrease in mirabegron plasma exposure with food that is independent of dose (50 or 100 mg) or gender, but dependent on meal composition; however, this does not warrant dose adjustment in clinical practice <sup>29</sup>. Pharmacokinetic changes observed in subjects with severe renal impairment or moderate hepatic impairment <sup>25</sup> mean that dose reduction is necessary.

### Clinical evidence of efficacy

Mirabegron has been studied extensively, with more than 10,000 subjects involved in research studies over approximately 10 years. The safety and efficacy was evaluated in five global trials (two in phase 2 and three in phase 3) comparing various doses of mirabegron, either with placebo or tolterodine.

BLOSSOM was a phase 2 proof of concept trial conducted in six European countries <sup>30</sup>. The study randomised subjects to mirabegron at doses of 100 or 150 mg twice daily (BID), placebo (BID), or tolterodine 4 mg extended release (ER) once daily for four weeks. The primary endpoint was change from baseline

to end-of-treatment in mean number of micturition episodes per 24 hours. Mirabegron was superior to placebo and tolterodine, with mean reduction in micturition frequency of 2.2, 1.2 and 1.5 respectively. Mirabegron was superior to placebo in terms of mean volume voided, mean number of incontinence episodes, nocturia episodes and urgency episodes in 24 hours. There was no significant difference found between 100mg and 150 mg twice daily doses.

The DRAGON study was a 12-week Phase 2B dose-ranging study conducted predominantly in Europe <sup>31</sup>. 919 patients were randomised in six arms: placebo, mirabegron at doses of 25, 50, 100 or 200 mg once daily, or tolterodine as an active comparator. A dose-dependent decrease in mean number of micturitions per 24 hours was seen with mirabegron, which was significant at the doses of 50mg and above as compared to placebo. 28% of people receiving mirabegron 50mg were classified as “responders” in terms of a reduction in voiding frequency (down to eight times daily or less). This compared with 19% for placebo and 19% for tolterodine. There were also significant improvements seen in secondary endpoints, such as mean number of urgency and urgency incontinence episodes, nocturia, and mean voided volume. Responses were evident at one week of treatment, with maximum efficacy gained at 8-12 weeks.

The Phase 3 development programme comprised three studies; SCORPIO, ARIES, and CAPRICORN. These were large-scale, 12-week, multicenter, randomized, double-blind, parallel-group studies undertaken in Europe, Australia, and North America. They looked at two co-primary efficacy endpoints; the change from baseline to endpoint in mean incontinence episodes and mean number of micturitions per 24 hours. The study populations were adults of at least 18 years

of age, with at least 8 micturitions per 24 hours, and at least three urgency episodes in their three day bladder diary, with or without urgency incontinence. Different doses of mirabegron were compared with placebo, and an active antimuscarinic comparator in some studies.

SCORPIO <sup>32</sup> recruited 1,978 OAB patients and showed statistically significant improvement with 50 and 100mg mirabegron in both the measures. Although improvement was also seen in the tolterodine 4mg ER arm, it was not statistically significant. Significant improvement was also seen in mean number of urgency episodes and mean voided volume with mirabegron 50mg compared with placebo.

ARIES enrolled 1,328 OAB patients, and significant improvement was seen in both co-primary end points, along with mean level of urgency, mean urgency incontinence episodes per 24 hours, and mean nocturia episodes <sup>33</sup>.

CAPRICORN included 1,306 patients, who were randomised to placebo, mirabegron 25mg or mirabegron 50mg <sup>34</sup>. Mean reductions in incontinence episodes were 1.36 and 1.38 for mirabegron 25 mg and 50 mg, comparing with 0.96 for the placebo group. Mean reductions in micturitions per 24 hours were 1.65 and 1.60 for mirabegron 25 mg and 50 mg respectively (1.18 for placebo). Mirabegron 50 mg demonstrated significantly greater improvements versus placebo in mean volume voided/micturition, and this was not seen for mirabegron 25 mg <sup>34</sup>.

Pooled analysis of the data from above trials reviewed outcomes of 3,542 patients randomised between placebo, mirabegron 50mg and mirabegron 100mg <sup>35</sup>. This showed the reduction in mean number of incontinence episodes per 24 hours

after 12 weeks of therapy was -1.10, -1.49 and -1.50 respectively. The equivalent reductions for number of micturitions per 24 hours were -1.20, -1.75 and -1.74<sup>35</sup>. The higher dose did not appear to achieve additional benefit. The active doses also showed benefits in “dry rates” (zero incontinence episodes per 24 hours), at 44.1% (mirabegron 50mg) and 46.4% (100mg) compared with 37.8% for placebo<sup>35</sup>. Statistically significant change in nocturia was seen, but the extent of clinical benefit is arguable (-0.55 voids per night for the active compound, -0.42 for placebo). Significant difference relative to placebo in these parameters was seen at four weeks.

Mirabegron 25mg and 50mg were also shown to be effective in older patients with OAB (>65 or >75 years), demonstrating improvements in the primary endpoints<sup>36</sup>.

Considering that antimuscarinic medications have long been the primary drug therapy for OAB, *post hoc* subgroup analysis looked at the effectiveness in treatment-naïve patients and those who had previously discontinued antimuscarinic treatment (either from lack of efficacy, or due to difficulty tolerating the medication)<sup>37</sup>. Response to mirabegron in terms of primary outcome measures was not affected by antecedent medication exposure (for those who discontinued due to poor efficacy), but it did significantly impact on response to the antimuscarinic active comparator. The placebo effect was found to be greater in the treatment-naïve patients. Further information on this will be given by the BEYOND study<sup>38</sup>, which studied 1,870 patients who were not satisfied by antimuscarinic therapy (on a treatment satisfaction Likert scale), and randomized them to either mirabegron 50mg or solifenacin 5mg.



Overall, onset of response appears to be achieved for efficacy and quality of life measures at one month <sup>39</sup>. Long term efficacy was evaluated in the TAURUS study, which was a randomized, double blind parallel group phase 3 trial, using mirabegron at doses of 50 or 100mg and tolterodine 4mg extended release as active comparator <sup>40</sup>. In this trial, 2,444 patients were recruited. Efficacy endpoints were secondary measures, with improvements in OAB symptoms for both doses (50 and 100mg) seen by one month, using various measures, and maintained throughout the follow up period

Health-related quality of life (HRQL) and treatment satisfaction were assessed in the mirabegron trials using various validated OAB-specific and general scales, such as the overactive bladder questionnaire (OAB-q) <sup>41</sup>, the patient perception of bladder condition (PPBC) <sup>42</sup> and a treatment satisfaction visual analog scale (TS-VAS). Significant improvement was demonstrated from baseline to final visit in these parameters of HRQL in all three of the main phase 3 studies.

In the DRAGON study <sup>31</sup>, International Consultation on Incontinence Questionnaire-Overactive Bladder (ICIQ-OAB) and ICIQ-OABqol questionnaires were used. Patient reported benefit was also evaluated, with the question “has the treatment been of any benefit to you?” The percentage of responders were 59.0%, 65%, 65.8% and 70.8% for 25, 50, 100 and 200mg mirabegron respectively, compared with 51% for placebo and 55% of the tolterodine group.

The studies included male patients, who generally made up between one quarter and one third of the study population in most of the reported studies, but the analyses did not separate findings according to gender.

## Safety and Tolerability

Mirabegron appears to have acceptable safety and tolerability in all the reported trials. In the BLOSSOM trial <sup>31</sup>, the incidence of treatment emergent adverse effects (TEAEs) was 39.2% with mirabegron, compared to 36.4% and 48.4% with placebo and tolterodine respectively. Most of the adverse effects were minor or moderate in severity. The most commonly reported side effects were gastrointestinal disorders (13.8%), followed by headache (6.9%). Dizziness and palpitations were more common in mirabegron groups than the tolterodine group. The discontinuation rates due to adverse effects were 4.6% and 7.7% for the mirabegron groups, compared to 1.5% in the placebo group and 3.1% in the tolterodine group.

In the DRAGON trial <sup>31</sup>, the incidence of serious adverse events was reported as <2% of patients across the treatment groups. The most common side effects reported were again gastrointestinal (7.2%-8.3% with mirabegron vs 5.3% with placebo), including constipation, dry mouth, dyspepsia and nausea. Incidence of dry mouth was higher with tolterodine (3.5%) than mirabegron (1.8-3.0%). A dose-dependent small rise in pulse rate was also noted with mirabegron; this was not associated with any cardiovascular side effect, with no difference found in ECG parameters and blood pressure across the treatment groups. Discontinuation due to side effects was low, at 3.0% for placebo (3.0%), 2.4-5.3% for mirabegron and 1.2% for tolterodine. There were no clinically significant episodes of acute retention observed with mirabegron.

Pooled safety data from SCORPIO, ARIES, and CAPRICORN showed that the overall incidence of TEAEs was similar across the treatment groups and there was no evidence of a dose-response relationship among the mirabegron treatment groups for overall rates of TEAEs (mirabegron 25 mg 48.6%, mirabegron 50 mg 47.1%, mirabegron 100 mg 43.3%, total mirabegron 46.0%, placebo 47.7% and tolterodine ER 4 mg 46.7%)<sup>35</sup>. The most common side effects noted in the mirabegron groups were hypertension (7.3%), nasopharyngitis (3.4%), and urinary tract infection (3.0%). Dry mouth occurred more commonly in the tolterodine group (2.0% for the total mirabegron groups vs. 2.1% for placebo and 10.1% for the tolterodine group). The discontinuation rates were; mirabegron 25 mg 3.9%, mirabegron 50 mg 3.9%, mirabegron 100 mg 3.7%, total mirabegron 3.8%, placebo 3.3%, and tolterodine ER 4 mg 4.4%.

In the 12-month TAURUS study, the incidence of TEAEs was similar across the mirabegron 50 mg (59.7%), mirabegron 100 mg (61.3%), and tolterodine ER 4 mg (62.6%) groups. Most of the side effects were of mild or moderate severity. The most frequent were hypertension, constipation, and headache, occurring at a similar incidence across treatment groups, and dry mouth. Dry mouth had a higher incidence in the tolterodine group (8.6%, versus mirabegron 2.3-2.8%). Discontinuations due to AEs were comparable across treatment groups, occurring in 6.4%, 5.9%, and 6.0% of patients receiving mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg, respectively.

In older patients, 49% of placebo patients, and 55% on active compound reported a treatment emergent adverse effect. The three main adverse effects on active

compound were hypertension, nasopharyngitis and urinary tract infection <sup>36</sup>. Dry mouth and constipation did not differ from placebo.

For men, in whom bladder outlet obstruction might be a feature due to benign prostate enlargement, the possibility of impairing voiding function as a consequence of administering medications to aid urine storage has to be considered. A urodynamic safety study was undertaken in 200 men receiving mirabegron 50 or 100mg or placebo for 12 weeks <sup>43</sup>. Maximum flow rate and detrusor pressure at maximum flow were not significantly impaired by active treatment. A small increase in post void residual was seen for mirabegron 100mg. Acute urinary retention occurred in one man on placebo and one on mirabegron 100mg. The proportion of patients experiencing  $\geq 150$  ml change from baseline in post void residual volume was lower in the mirabegron groups compared with tolterodine: mirabegron 25 mg (0%), mirabegron 50 mg (0.3%), mirabegron 100 mg (0.4%), placebo (0.7%), and tolterodine ER 4 mg (0.8%) in the pooled analysis of the phase III trials <sup>35</sup>.

Mirabegron was shown not to raise intraocular pressure (IOP) after treatment with 100mg daily for 8 weeks in healthy volunteers <sup>44</sup>, which is advantageous when considering that closed-angle glaucoma is a contra-indication to antimuscarinic therapy.

### Combination therapy

Management of LUTS is increasingly reliant on combination pharmaceutical therapy, and the introduction of a new drug class for OAB offers further

opportunities for combinations aiming to increase efficacy or reduce side effects. The SYMPHONY study <sup>45</sup> was a dose ranging phase 2 study using a range of permutations combining mirabegron with solifenacin. Several combination doses achieved greater improvements in mean voided volume, micturition frequency, and urgency than solifenacin monotherapy. The BESIDE study <sup>46</sup> has recently completed recruitment, and was designed to see if adding mirabegron to an antimuscarinic treatment (solifenacin) will be more effective in controlling incontinence than when using the antimuscarinic treatment alone.

In male LUTS, combinations of antimuscarinic medication and alpha adrenergic blockers are routinely used in refractory cases (for example solifenacin and tamsulosin <sup>47</sup>). Combining mirabegron with alpha adrenergic blockers is likely to be considered in developing the therapeutic area. Efficacy assessments for such combinations have recently been reported in men receiving mirabegron with tamsulosin (0.2mg), in whom the OAB Symptom Score (OABSS) fell by -2.21 for the combination group and by -0.87 in the tamsulosin monotherapy group <sup>48</sup>. The safety aspects of combining mirabegron with tamsulosin have previously been reported in a separate study <sup>28</sup>.

## Conclusions

Mirabegron is a first-in-class  $\beta$ -3 agonist for treatment of OAB in women or men, which appears to have good efficacy and tolerability. It can be used in patients who have discontinued antimuscarinic therapy, or who have contraindications for antimuscarinics. Development of combination therapies may further extend the management options in OAB in the future.

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